PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Impact of Temperature Extremes on Mortality：a time-series study in Jinan, China
AUTHORS	Han, Jing; Liu, Shouqin; Zhang, Jun; Zhou, Lin; Fang, Qiaoling; Zhang, Ji; Zhang, Ying

VERSION 1 - REVIEW

REVIEWER	Professor Peng Bi The University of Adelaide, Australia
REVIEW RETURNED	09-Nov-2016

GENERAL COMMENTS	This study has addressed an important public health issue in the context of climate change and the results from this project will provide significant implications to policy-makers and public health practitioners. This study assessed the impact of extreme weather events, both cold and heat, on the daily mortality in a temperate city of China. The study design is sound ecological study, the analytic approaches are correct, the results are convincing, and the references are updated. I have listed my minor suggestions below to help the authors to refine their manuscript: 1) Study limitations: Ozone is another impact factor which would have a significant impact on population health. I understand that the data might be not available from the study city--I suggest that this should be mentioned and acknowledged in the discussion section; 2) Public health implications from the study results: I was wondering whether the authors could make the recommendations in details in the discussion section, targeting on policy and guidance development, capacity building, community education and engagement etc.

REVIEWER	Ben Armstrong LSHTM, UK
REVIEW RETURNED	03-Jan-2017

GENERAL COMMENTS	Within its limited scope, I believe that this paper delivers valid evidence on impact of temperature extremes on mortality, subject to confirmation of some details. The limitations are substantial, so that addition to existing knowledge is very limited, but I understand that this Journal does not consider this.

	1. Unless there are some innovative aspects, weather-mortality studies of single cities are hard to justify reading given the many multi-city studies. This limitation is noted. 2. I am unsure if Jinan was included in Ma's publications on weather-mortality associations in 66 communities in China (this should be clarified), but certainly others with similar climates were, so that the value added by this study is not without further explanation demonstrated. The previous publication on heat waves in Jinan using slightly fewer years of mortality data (ref 20) further limits what is new in the submitted paper. 3. Describing the risk in heat and cold waves can give some insights on the dependence of mortality on temperature, but, at least in the simple approach of this paper, to a very limited extent. Many studies have demonstrated that adverse impacts of non-optimal temperatures extend much beyond these waves, and so purely wave studies can only describe part of the total effect. Wave studies can elucidate the effect of duration of extreme temperatures, but in this paper this is not distinguished from the expected simpler effect of the extent of the extremity. (Many papers, including the Ma paper cited did explore the "added" wave=duration effect). The distinction between the approach used in the submitted paper and the "added wave effect" approach of Ma and several other papers on waves should be stated. 4. With one exception (see 8 below) results were broadly in line with the many other published studies of heat and cold Vs mortality in China and elsewhere. A degree of reassurance, but nothing really new. (No response required.) Minor issues 5. The statement: "Long-term trend and seasonal various, day of week, relative humidity, ambient temperature and autocorrelation were controlled in the model as confounders" encourages me to believe that appropriate methods were used, but without detail of parametric form this cannot be sure. Also, it needs stating whether over-dispersion was present, and if so how allowed for. 6. The Poisson regression seems to me to be better in many respects to the cross-correlations and comparison of means, such that these seem just distractions. Consider dropping. 7. The emphasis on statistical significance is too strong. In particular, comparing RRs in sub-groups is not helped by this. For example the RRs for cold in COPD is slightly higher than that for CVD: cardiovascular (RR1.03, 95%CI: 1.00-1.06), COPD (RR1.04, 95%CI: 0.92-1.17). That the CVD but not the COPD RR is "significant" is not evidence that the cold RR is higher for CVD than COPD. 8. The one result I found surprising, and thus interesting, was that the RR for cold was HIGHER in the <65 than 65+ age group, with CIs in this instance indicating more than suggestive evidence for a difference. This is unusual and worth noting in discussion. 9. Although exploring the role of pollution would be useful, it probably should not, if available, be considered as a simple confounder. The commentaries of Reid (2012 EHP) and Buckley (2014 Epidemiol) explain this. 10. References 18 and 23 seem identical.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Professor Peng Bi
Institution and Country: The University of Adelaide, Australia
Competing Interests: none declared

This study has addressed an important public health issue in the context of climate change and the results from this project will provide significant implications to policy-makers and public health practitioners.

This study assessed the impact of extreme weather events, both cold and heat, on the daily mortality in a temperate city of China. The study design is sound ecological study, the analytic approaches are correct, the results are convincing, and the references are updated.

I have listed my minor suggestions below to help the authors to refine their manuscript:

1) Study limitations: Ozone is another impact factor which would have a significant impact on population health. I understand that the data might be not available from the study city--I suggest that this should be mentioned and acknowledged in the discussion section;
We agree with the reviewer on this point. Ozone is an important factor that contributes to public health, particularly the potential interaction with temperature extremes. However, the data of ozone over the study period were not available as guessed by the reviewer. Therefore, we have discussed this issue in the revision on page 8.
“Second, data of air pollution, e.g. ozone, were not available over the study period. In previous studies, the estimated temperature effects were slightly reduced or not changed when air pollution including ozone was controlled for10, 25. Some studies also found a potential interaction between temperature and ozone30. However, there are also studies suggesting that the effects of air pollution on mortality could be much smaller than the temperature effects31-32. Thus, the relationship that we detected between mortality and the temperature extremes might not be substantially confounded by the effects of air pollution. ”

2) Public health implications from the study results: I was wondering whether the authors could make the recommendations in details in the discussion section, targeting on policy and guidance development, capacity building, community education and engagement etc.
Discussion on public health implications of the study has been given with more details on page 8.
“Given that climate change will bring more temperature extremes including cold spell, our study has public health implications for policy and practice for government at all levels, as well as community capacity building. Specifically, findings of our study can assist in development of adaptive strategies and policies with a focus on identified vulnerable populations in the community, including the refinement of current public health emergency response plans to focus on both very hot and very cold temperatures. It could also inform the development of clinical guidelines and training programs to doctors in order to improve health service during extreme temperature events, with a better understanding of the pathophysiological mechanisms in mediating heat and cold health effects. Building community resilience could also be supported with better preparation to reduce the number of temperature-related deaths.”

Reviewer: 2
Reviewer Name: Ben Armstrong
Institution and Country: LSHTM, UK
Competing Interests: None

Within its limited scope, I believe that this paper delivers valid evidence on impact of temperature

extremes on mortality, subject to confirmation of some details. The limitations are substantial, so that addition to existing knowledge is very limited, but I understand that this Journal does not consider this.

1.Unless there are some innovative aspects, weather-mortality studies of single cities are hard to justify reading given the many multi-city studies. This limitation is noted.
Firstly, we have acknowledged the limitation with data from one city on page 8. Although generalization of the study findings would be limited, we also acknowledge the importance of local studies that provided evidence for decision making in policy and practice for local communities. In addition, findings from previous studies demonstrate large geographical heterogeneity of the effects of temperature extremes on mortality. The study city, Jinan, has a unique exposure to temperature extremes in China, and was not included in the previous multi-city studies. Most temperature-health studies in China focused on heat wave only. Our findings have demonstrated cold spell could contribute to increased risk of deaths in Jinan, which should not be ignored in health preparation. Our findings have provided public health implications for policy makers, clinical training and building community resilience. Details have been added in the new paragraph on page 8.
“Given that climate change will bring more temperature extremes including cold spell, our study has public health implications for policy and practice for government at all levels, as well as community capacity building. Specifically, findings of our study can assist in development of adaptive strategies and policies with a focus on identified vulnerable populations in the community, including the refinement of current public health emergency response plans to focus on both very hot and very cold temperatures. It could also inform the development of clinical guidelines and training programs to doctors in order to improve health service during extreme temperature events, with a better understanding of the pathophysiological mechanisms in mediating heat and cold health effects. Building community resilience could also be supported with better preparation to reduce the number of temperature-related deaths.
Some limitations of the study should be acknowledged. First, the data were only from one city, generalization of the results to other regions should be cautious. However, we also recognize the importance of local studies to assist decision making for local communities. The lessons learnt from Jinan could provide more evidence for other regions with similar conditions in China.”

2.I am unsure if Jinan was included in Ma’s publications on weather-mortality associations in 66 communities in China (this should be clarified), but certainly others with similar climates were, so that the value added by this study is not without further explanation demonstrated. The previous publication on heat waves in Jinan using slightly fewer years of mortality data (ref 20) further limits what is new in the submitted paper.
Jinan was not included in Ma’s paper. We have clarified this issue in the Introduction on page 2.
“However, there has been not a clear picture on the effects of both extreme cold and hot temperatures on mortality in the city, which was not included in the previous publication on weather-mortality in 66 communities in China either.”

Therefore, our study provided more evidence regarding temperature-health research. Besides, our study focused on not only heat wave but also cold spell on daily mortality. Few studies reported the relationship in China like our study no matter in a single city or multi-cities study.

Compared with our previous study on heat wave and mortality in Jinan, the advantages of this study included: 1) a larger and more recent dataset with more categories of cause of deaths were used, 2) effects of cold spell was analyzed in addition to heat waves, and 3) vulnerability was examined based on age and gender. This issue has been clarified in Introduction on page 2.
“ Our previous study in Jinan found that heat waves significantly increased the risk of mortality and caused 24.88 % excess non-accidental deaths.17 This study uses more recent data to investigate the effect of both heat wave and cold spell on daily number of deaths in Jinan. Furthermore, we have

explored vulnerable populations to temperature extremes."

3.Describing the risk in heat and cold waves can give some insights on the dependence of mortality on temperature, but, at least in the simple approach of this paper, to a very limited extent. Many studies have demonstrated that adverse impacts of non-optimal temperatures extend much beyond these waves, and so purely wave studies can only describe part of the total effect. Wave studies can elucidate the effect of duration of extreme temperatures, but in this paper this is not distinguished from the expected simpler effect of the extent of the extremity. (Many papers, including the Ma paper cited did explore the "added" wave=duration effect). The distinction between the approach used in the submitted paper and the "added wave effect" approach of Ma and several other papers on waves should be stated.

First of all, this is not a 'purely wave study' because we did investigate the temperature-mortality relationship and population vulnerability in order to get a better understanding of the whole picture. Secondly, we do acknowledge that there are studies examined the effects of various characteristics of heat waves, e.g. duration, time of seasons and maximum temperatures of waves. We did not include such analysis in this paper due to the consideration of the following points, 1) similar characteristics of the observed waves in this study area, which may lead to non-significant risk differences anyway; 2) risk of "excess deaths" due to heat waves were estimated by our previous studies; and 3) potential distractions that may be caused by too many results in this paper.

According to the reviewer's comments, we have clarified this issue on page 3 and added discussions on the comparison between our study and Ma's study on page 7.

"However, our estimates of increased mortality risk during heat waves are not as high as those from the previous study on temperature and mortality in China. 15 There are several possible reasons for this. First of all, techniques used to estimate increased risks for mortality varied across the studies. We applied a time-series adjusted Poisson regression rather than a time-series regression model combined distributed lag nonlinear model (DLNM) used in Ma's studies. The DLNM can estimate cumulative effect in the existence of delayed contributions. But they used cumulative excess mortality risk of heat wave only at 0-1 lag days. Instead, we have examined the risk at various lag values. Moreover, Jinan often has particularly very hot summer days with unique geographic and environmental situations. Local residents may have developed adaptive behaviors to heat, which could contribute to a reduced mortality risk."

4. With one exception (see 8 below) results were broadly in line with the many other published studies of heat and cold Vs mortality in China and elsewhere. A degree of reassurance, but nothing really new. (No response required.)

We have added more details regarding public health implications this study can provide on page 8. Please refer to responses to your question 1.

Minor issues

5.The statement: "Long-term trend and seasonal various, day of week, relative humidity, ambient temperature and autocorrelation were controlled in the model as confounders" encourages me to believe that appropriate methods were used, but without detail of parametric form this cannot be sure. Also, it needs stating whether over-dispersion was present, and if so how allowed for.

More details of the regression model have been provided with the parametric equation. No over-dispersion was detected in our data. We have clarified these issues in Methods on page 3.

"Time-series adjusted Poisson regression was applied to quantify the impacts of cold spell/heat wave on daily number of deaths at different lag days. Contributing factors, such as long-term and seasonal trends, day of week (DOW), relative humidity (RH) and ambient temperature were controlled in the model as potential confounders. No over-dispersion was detected in our data, and the model used in the analysis can be described as:

$$Log[E(Yt)] = \alpha + \beta Tmint + \eta DOWt + \gamma Stratat + \lambda RHt + \delta EDt$$

where t is the day of the observation; Yt is the observed daily death counts on day t; α is the intercept; Tmin is mean temperature on day t, and βis vector of coefficients; DOW is day of the week on day t, and η is vector of coefficients; Stratat is a categorical variable of the year and calendar month used to control for season and trends, andγ is vector of coefficients. RH is relative humidity on day t, and λis vector of coefficients; ED(exposure days)t is a binary variable that is "1" if day t was a extreme temperature exposure days(cold spell/heat wave), and δis the coefficient.
Relative Risks were estimated by the regression. Population vulnerability was examined based on age and gender of deceased cases.

6.The Poisson regression seems to me to be better in many respects to the cross-correlations and comparison of means, such that these seem just distractions. Consider dropping.
Cross-correlation analysis was used to detect appropriate lag values for the regression. The comparison of means was essential to provide a simple but direct picture of the extent of death risks from exposure and non-exposure days. If there was no significant difference from the comparison, then no need to perform further regression models. We hope this logical presentation of our analyses and results has addressed your concerns appropriately. No dropping of results was made.

7.The emphasis on statistical significance is too strong. In particular, comparing RRs in sub-groups is not helped by this. For example the RRs for cold in COPD is slightly higher than that for CVD: cardiovascular (RR1.03, 95%CI: 1.00-1.06), COPD (RR1.04, 95%CI: 0.92-1.17). That the CVD but not the COPD RR is "significant" is not evidence that the cold RR is higher for CVD than COPD.
We have revised relevant sentences in the discussion on page 5.
"The risk of deaths related to heat waves also increased for non-accidental (RR1.02, 95%CI: 1.00-1.05), cardiovascular (RR1.03, 95%CI: 1.00-1.06) and stroke (RR1.06, 95%CI: 1.00-1.13) but not for deaths due to respiratory (RR1.02, 95%CI: 0.93-1.11) and COPD (RR1.04, 95%CI: 0.92-1.17)."

8.The one result I found surprising, and thus interesting, was that the RR for cold was HIGHER in the <65 than 65+ age group, with CIs in this instance indicating more than suggestive evidence for a difference. This is unusual and worth noting in discussion.
We have added discussion about this finding and possible explanations on page 7/8.
"One interesting finding from our study is the higher vulnerability to cold among the younger age group (<65 years), compared with the older group (over 65 years). The finding sounds different from previous studies that reported older people (over 65 years or 75 years) might be the most vulnerable24-25. It indicates that population vulnerability to cold spells could vary depending on various study settings. Similar evidence in Ireland shows that young adults (18-64 years) with respiratory disease might be the most susceptible to cold related deaths. 24 Kysely's study conducted in the Czech Republic also reported cold spells had the greatest effect on young adult men (25–59 years) with CVD. 26 Occupational exposure might attribute to our finding, given that older people tended to stay indoors during very cold days, and thus avoided direct exposure to low ambient temperatures. In addition, adaptive behaviors might be more likely taken by older residents in Jinan because of very cold winters in the history. More research is required to identify underlying reasons of the population vulnerability to cold in Jinan."

9.Although exploring the role of pollution would be useful, it probably should not, if available, be considered as a simple confounder. The commentaries of Reid (2012 EHP) and Buckley (2014 Epidemiol) explain this.
No air pollution data was available for the study period. As the reviewer said, it could be a minor confounder in the analysis if we did include the data. We have added more discussion to address this issue in the limitation on page 8.
"Data of air pollution, e.g. ozone, were not available over the study period. In previous studies, the estimated temperature effects were slightly reduced or not changed when air pollution including

ozone was controlled for. 10, 27 Some studies also found a potential interaction between temperature and ozone. 33 However, there are also studies suggesting that the effects of air pollution on mortality could be much smaller than the temperature effects. 34-35 Thus, the relationship that we detected between mortality and the temperature extremes might not be substantially confounded by the effects of air pollution."

10.References 18 and 23 seem identical.
This has been corrected. We have double-checked all the references to avoid any mistakes.

VERSION 2 – REVIEW

REVIEWER	Ben Armstrong LSHTM, UK
REVIEW RETURNED	25-Jan-2017

GENERAL COMMENTS	I have reviewed the revised MS and response letter and see no further issues needing to be addressed except one, the response to my previous comment 7. 7.The emphasis on statistical significance is too strong. In particular, comparing RRs in sub-groups is not helped by this. For example the RRs for cold in COPD is slightly higher than that for CVD: cardiovascular (RR1.03, 95%CI: 1.00-1.06), COPD (RR1.04, 95%CI: 0.92-1.17). That the CVD but not the COPD RR is "significant" is not evidence that the cold RR is higher for CVD than COPD. We have revised relevant sentences in the discussion on page 5. "The risk of deaths related to heat waves also increased for non-accidental (RR1.02, 95%CI: 1.00-1.05), cardiovascular (RR1.03, 95%CI: 1.00-1.06) and stroke (RR1.06, 95%CI: 1.00-1.13) but not for deaths due to respiratory (RR1.02, 95%CI: 0.93-1.11) and COPD (RR1.04, 95%CI: 0.92-1.17)." Here the authors seem to me to have even more explicitly proposed the (wrong) interpretation that there is evidence that the heat wave risk is higher for, say, CVD than, say, COPD. A non-significant association is not the same as no association. Re-instating the old text would be preferable.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Ben Armstrong
Institution and Country: lshtm, uk
Competing Interests: none

I have reviewed the revised MS and response letter and see no further issues needing to be addressed except one, the response to my previous comment 7.
7.The emphasis on statistical significance is too strong. In particular, comparing RRs in sub-groups is not helped by this. For example the RRs for cold in COPD is slightly higher than that for CVD: cardiovascular (RR1.03, 95%CI: 1.00-1.06), COPD (RR1.04, 95%CI: 0.92-1.17). That the CVD but not the COPD RR is "significant" is not evidence that the cold RR is higher for CVD than COPD.
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"The risk of deaths related to heat waves also increased for non-accidental (RR1.02, 95%CI: 1.00-1.05), cardiovascular (RR1.03, 95%CI: 1.00-1.06) and stroke (RR1.06, 95%CI: 1.00-1.13) but not for deaths due to respiratory (RR1.02, 95%CI: 0.93-1.11) and COPD (RR1.04, 95%CI: 0.92-1.17)."
Here the authors seem to me to have even more explicitly proposed the (wrong) interpretation that

there is evidence that the heat wave risk is higher for, say, CVD than, say, COPD. A non-significant association is not the same as no association. Re-instating the old text would be preferable.
*We have revised relevant sentences as your suggestion in the result section on page 6.
The risk of deaths related to heat waves increased significantly for non-accidental (RR1.02, 95%CI: 1.00-1.05), cardiovascular (RR1.03, 95%CI: 1.00-1.06) and stroke (RR1.06, 95%CI: 1.00-1.13). Deaths of respiratory (RR1.02, 95%CI: 0.93-1.11) and COPD (RR1.04, 95%CI: 0.92-1.17) also increased during the heat waves, but the impact was not statistically significant.